REMARKS

Applicants submit that the pending claims, including the claims amended and newly presented in response to the Office Action, are in condition for allowance.

A. Claims 35-39, 41, 42, 45, 46, And 55-59 Are Not Obvious Over Need

Examiner rejected claims 35-39, 41, 42, 45, 46, and 55-59 as unpatentable over the abstract of the Need et al. reference. Examiner states that the abstract of the Need et al. reference teaches the combination of ovarian hormones (specifically norethindrone) and a vitamin D compound (specifically calcitriol). The Examiner rejected Applicants' composition claims as obvious over the Need reference. Applicants submit herewith at Tab A a copy of the full Need reference for consideration along with the abstract.

Applicants submit that the instant claims fall into three different broad categories for purposes of responding to this Office Action. The first group of claims (35-44) is drawn to ***single unit dosages*** containing a progestin and a Vitamin D compound. The second group of claims (45-54) is drawn to compositions that are ***contraceptively*** effective. The third group of claims (55-73) is drawn to ***hormone replacement therapy*** regimens for administration to post-menopausal women. Applicants have amended the third group of claims to include dosages of Vitamin D that are far higher than the dosages found in the Need reference as described below.

1. Need Does Not Teach Or Motivate Single Unit Dosages And Thus Does Not Render Obvious The First Group Of Claims (35-44)

Applicants submit that the first group of claims requiring single unit dosages (claims 35-39, 41, and 42) are not obvious over the Need abstract or the full Need reference. As an initial matter, the Need reference absolutely does not teach a ***single unit dosage*** containing a progestin and a Vitamin D compound as required by the claims. Thus, Need could only render

these claims obvious if it provided some motivation to take the further, undisclosed step of combining a progestin and a Vitamin D compound into a single unit dosage. In order to be held to be obvious using a single reference, there must be a motivation to modify the teachings of a reference to arrive at the claimed invention. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed.Cir. 2000). However, neither the Need abstract nor the full Need reference provide any such motivation. Rather, Need teaches away from such a combination.

The Need abstract contains no teaching of a single unit dosage of progestin and Vitamin D. The full Need reference shows that the study involved the administration of ***separate*** pills of various compounds. Two of those compounds were a ***separate pill*** of progestin hormone and a ***separate*** pill of Vitamin D compound. Need administered the separate pills in various combinations to post-menopausal women with osteoporosis to determine if there was a benefit from the various therapies, including some combination therapies. With respect to combining progestin and Vitamin D, Need found that there was absolutely no benefit.

First, as stated in the Need abstract, Need combined (1) calcium with progestin and compared the results to (2) the combination of Vitamin D, calcium and a progestin hormone. The abstract of the Need reference states that there was no benefit to combining Vitamin D with progestin: "[c]alcium and ovarian hormones ***with or without calcitriol***, caused a small non-significant rise in forearm mineral density." In other words, one obtained the "small non-significant rise in forearm mineral density" by just combining calcium with progestin. The further addition of Vitamin D provided no benefit.

As seen in Figure 1 of the full Need reference, the combination of progestin with calcium showed some slight benefit, However, there was no added benefit when Vitamin D was added to the progestin/calcium combination (see Need et al. p. 277, full study attached). Thus,

Need teaches no benefit of combining progestin with Vitamin D. Without any benefit to the combination, one would certainly have no motivation to combine these compounds in a single unit dosage. Because there was no benefit shown in the Need study from combining progestin and Vitamin D, there would be no motivation to combine the compounds into a single unit dosage; thus, the first group of claims regarding single unit dosages would not be obvious.

2. Need Does Not Teach Or Even Suggest Contraceptively Effective Compositions And Thus Does Not Render Obvious The Second Group Of Claims (45-54)

Applicants also submit that claims 45 and 46, from the second group of claims, are not obvious under the Need reference because the instant claims are drawn to compositions that are contraceptively effective. The combinations in the Need study were administered as hormone replacement therapies to post-menopausal, non-ovulating women whose average age was 61.5 to 65.7 with a SEM of +/- 1.5-2.5 years. The combinations were being tested for their efficacy in increasing bone density for non-ovulating, ***post***-menopausal women. Therefore, there would be no motivation from the teaching of make ***contraceptively*** effective combinations. Thus, the second group of claims regarding regimens that are contraceptively effective are not obvious under Need.

3. Need Does Not Teach The Increased Dosages Of Vitamin D That The Third Group Of Claims (55-73) Are Drawn To And The Applicants' Claims Are Therefore Distinguishable

Applicants submit that claims 55-59, part of the third set of claims regarding hormone replacement therapy, are not obvious and to the extent the claims were anticipated, they have been amended. Applicants submit that the third group of claims are distinguishable from the Need reference because Need does not teach the use of a vitamin D compound with progestin alone. Need teaches a vitamin D compound with calcium and vitamin D with calcium and a

progestin. Need shows no added benefit of adding progestin to the vitamin D and calcium composition in the studies on post-menopausal women. Therefore, there would be no motivation from Need to use vitamin D and progestin only in such a population.

In addition, Applicants submit that there would be no motivation from Need to increase Vitamin D dosages to the levels in the amended and newly presented claims if adding vitamin D did not provide an additional benefit to non-ovulating women. Applicants submit that their Vitamin D dosages are significantly higher than the dosages used in the Need study. For the claims measured in mg/kg, the dosage ranges of the amended claims would all fall within 0.006 mg and 60 mg (assuming the average weight of a woman is 60kg)—much greater than the 0.25 microgram (0.00025 mg) dose of Vitamin D in the Need reference. The newly presented claims for dosages in I.U. are also much greater than 0.25 microgram dose in Need. The accepted value for one I.U. for Vitamin D3 is 0.025 micrograms, so the newly presented claims would be at the least 10 micrograms—400 times greater than the Need study.

B. Claims Are Three Different Broad Categories And Are Not Duplicative

Examiner rejected claims 35 and 59 as duplicative of claim 49. Applicants submit that claim 49, part of the second group of claims, is limited to a regimen that is contraceptively effective, while claim 59, part of the third group of claims, is limited to a hormone replacement therapy regimen for administration to post-menopausal women. Claim 35 is drawn to a single unit dosage that is not limited to a contraceptive compositions or hormone replacement therapy.

Examiner rejects claim 45 as duplicative of claim 55 and rejects claim 46 as duplicative of 56. Applicants submit that Claim 55, part of the third group of claims, is limited to a hormone replacement therapy for administration to post-menopausal women, while claim 45, part of the second group of claims, is limited to a composition that is contraceptively

effective. Likewise, claim 56 is limited to a hormone replacement therapy, while claim 46 is limited to a composition that is contraceptively effective.

Conclusions

Applicants respectfully request that claims 35-39, 41, 42, 45, 46, 49, 55-59, and 65-73 be allowed for the reasons states above. Please charge any fees associated with this Amendment to Deposit Account No. 18-1942.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE

I certify that this document and authorization to charge deposit account is being facsimile transmitted to the United States Patent and Trademark Office (Fax. No. (703) 872-9306) on February 9, 2004.

Dated: 2/9/04

Raymond N. Nimrod

TAB A

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Comparison of calcium, calcitriol, ovarian hormones and nandrolone in the treatment of osteoporosis

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Most therapy for osteoporosis has been aimed at decreasing bone resorption and is capable of preventing further bone lost. Recently, anabolic steroids have been claimed to cause increased bone mass in osteoporosis, but the mechanism for this effect is not understood. In this study calcium, and calcium with calcitriol, caused a slowing of forearm bone mineral loss. Calcium and ovarian hormones, with or without calcitriol, caused a small non-significant rise in forearm mineral density, and nandrolone decanoate 50 mg intramuscularly, every 2 or 3 weeks caused a significant rise in forearm mineral density (+15.9 ± 2.4 mg/ml/yr and +13.7 ± 3.4 mg/ml/yr, respectively). The 3-weekly regime caused few side effects and is considered the optimal dose. The striking rise in bone density in patients in whom bone resorption was controlled before therapy, suggests that anabolic steroids can increase the bone formation rate.

(Key words: Osteoporosis, Anabolic steroids, Ovarian hormones, Calcium)

Introduction

We have previously reported a significant fall in urinary hydroxyproline when calcium supplements are administered to osteoporotic patients with normal calcium absorption, and a comparable fall if calcitriol is added to the regime in cases with calcium malabsorption [1,2]. Similar findings, indicating a fall in bone resorption, have been reported with oestrogen and progestagen therapy. This anti-resorptive therapy is accompanied, however, by a fall in plasma alkaline phosphatase activity [1,3] which indicates, we believe, a decrease in bone formation in response to the fall in bone resorption. This response may offset, to some degree, the beneficial effects of anti-resorptive therapy. There is no generally accepted way of increasing the bone formation rate, although vigorous exercise and fluoride therapy have been claimed to be useful [4]. In this regard, it may be worth remembering Albright's hypothesis

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that osteoporosis is entirely a result of decreased bone formation as a result of insufficient androgen production in later life [5]. While this is almost certainly wrong, Albright was able to demonstrate a positive effect of testosterone on calcium balance. The side effects of treatment with this hormone, however, made it unsuitable for use in post-menopausal women. Since then, anabolic steroids have been developed which have the anabolic effects of testosterone without the virilising effects [6]. In this paper we compare the effects on forearm bone density of anti-resorptive therapy (calcium, calcitriol and ovarian hormones) and anabolic steroid therapy in patients with osteoporosis.

Patients and methods

Patients with varying degrees of osteoporosis were classified as normal absorbers or malabsorbers of calcium by a radiocalcium absorption test [7], and malabsorbers were given calcitriol (Rocaltrol, Roche) 0.25 μg daily together with a calcium supplement (Sandocal, Sandoz) 1 g daily. Patients with increased bone resorption, measured by the fasting urinary hydroxyproline/creatinine were given either calcium alone or a combination of calcium and hormones (mainly norethisterone 5 mg/day). Those patients with normal bone resorption, and some whose bone resorption had been normalised by the above therapy, were treated with 50 mg of nandrolone decanoate (Deca-Durabolin, Organon) intramuscularly at intervals of either 2 or 3 weeks.

Forearm mineral content (FMC) was measured by the Molsgaard Bone Mineral Analyzer at approximately 4-monthly intervals and expressed as forearm mineral density (FMD) by dividing by the calculated cross-sectional area of the ulna and radius [8]. Subsequent FMC measurements were divided by the initial cross-sectional area to give sequential measurements of FMD. The number of cases in each group, their ages and initial forearm mineral densities are shown in Table I. Comparisons between groups were made using Student's *t*-test for unpaired data. Rates of change were time-weighted by entering each rate in the sum as many times as there were months of observation. The mean time-weighted rates were then compared using Student's unpaired *t*-test.

TABLE I

MEAN AGES AND INITIAL FMD IN THE VARIOUS TREATMENT GROUPS DESCRIBED IN THE TEXT

Therapy	Number of cases	Mean age (yr ± SEM)	Initial FMD (mg/ml ± SEM)
Calcium	38	65.7 ± 1.5	302 ± 8
Calcium + Hormones	26	61.5 ± 1.5	296 ± 13
$1,25(OH)_2D$ + Calcium	37	67.6 ± 1.3	294 ± 10
$1,25(OH)_2D$ + Ca + Hormones	10	63.7 ± 2.5	297 ± 30
Nandrolone 2-weekly	42	62.6 ± 1.2	314 ± 12
Nandrolone 3-weekly	38	64.8 ± 1.5	298 ± 11

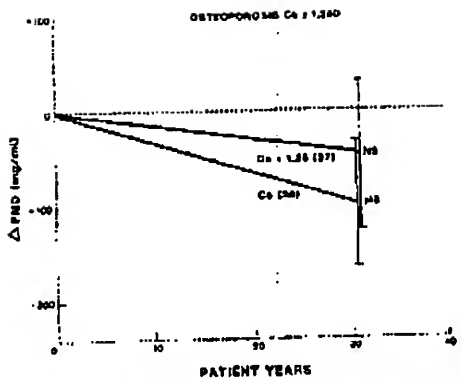

Fig. 1. Cusum plot of change in FMD with time in osteoporotic patients given calcium alone (1 g/day) or calcium with calcitriol (0.25 μg/day) The number of patients in each group is given in parentheses.

Results

There was a non-significant loss of bone in the patients treated with calcium alone (-3.3 ± 2.2 mg/ml/yr) and in those treated with calcium and calcitriol (-1.6 ± 2.5 mg/ml/yr; Fig. 1). There was a non-significant gain of bone in each of the two groups who received hormones together with calcium ($+4.4 \pm 5.2$ mg/ml/yr) or calcitriol ($+3.9 \pm 6.4$ mg/ml/yr; Fig. 2).

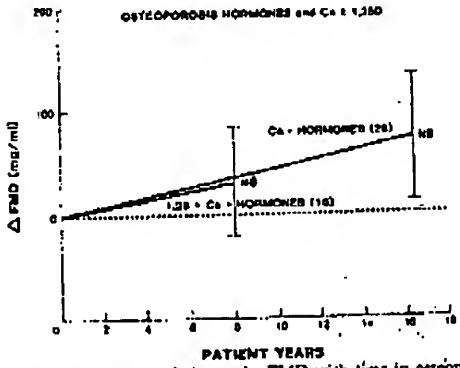

Fig. 2. Cusum plot of change in FMD with time in osteoporotic patients given calcium (1 g/day) with hormones or calcium with hormones and calcitriol (0.25 μg/day). The number of patients in each group is given in parentheses.

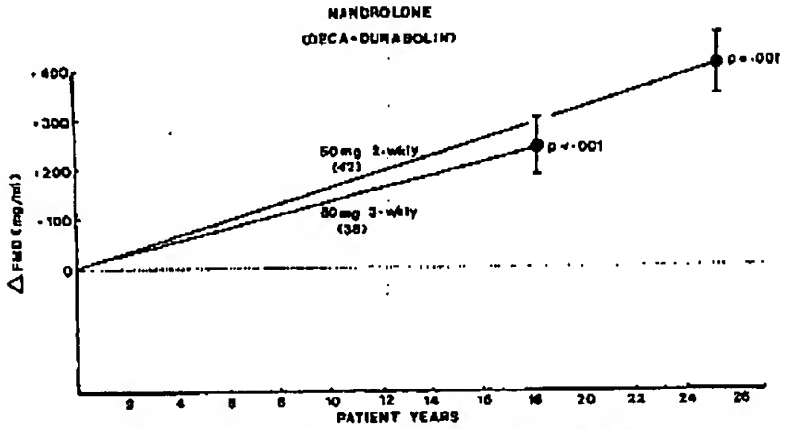

Fig. 3. Cusum plot of change in FMD with time in osteoporotic patients given nandrolone decanoate 50 mg intramuscularly at intervals of either 2 or 3 weeks. The number of patients in each group is given in parentheses.

There was a highly significant increase in FMD in the 42 patients given nandrolone every 2 weeks ($+15.9 \pm 2.4$ mg/ml/yr; $P < 0.01$) and in the 38 patients given nandrolone every 3 weeks ($+13.7 \pm 3.4$ mg/ml/yr; $P < 0.001$; Fig. 3). The difference between these rates of change is not significant, so the changes for all patients receiving nandrolone as sole therapy were pooled and compared with the changes in those given nandrolone together with anti-resorptive treatment. The increase for those on nandrolone alone was 21.1 ± 1.8 mg/ml/yr ($P < 0.001$) and for those given a combination including nandrolone 9.2 ± 2.8 mg/ml/yr ($P < 0.001$). The difference between these two rates is highly significant ($P < 0.001$) and the two groups were comparable in their initial mean FMD (305 ± 10 mg/ml and 310 ± 13 mg/ml, respectively). Hoarseness of the voice developed in 20 of the 42 patients given nandrolone every 2 weeks (48%) and in 2 out of the 38 given nandrolone every 3 weeks (5%) ($P < 0.001$). The mean duration of nandrolone therapy in each group was 7.2 and 5.2 mth, respectively.

Discussion

The most striking finding in this study is the highly significant rise in FMD in those patients given nandrolone, whether given alone or in combination with other therapy. In those patients given calcium or calcium with calcitriol there was probably some slowing of bone loss, as the expected rate of loss in normal post-menopausal women in Adelaide is 6 mg/ml/lyr (unpublished data). The most rapid loss among our treated patients was 3.3 mg/mly/yr and the rate of loss in

untreated osteoporotic patients, we expect, is much higher. In those patients given progestagen or oestrogen with or without calcium or without calcium or calcitriol there was a small gain in bone, but overall the anti-resorptive therapies appear to do little more than hold the bone status constant.

Nandrolone has been used for over 20 yr to treat osteoporosis, but there is a surprising lack of data on its effectiveness in this condition. Previous authors have found no evidence of biochemical [9] or radiological [10] change during anabolic steroid therapy, but recently some positive reports have appeared. Measurements of total body calcium by neutron activation analysis [11,12] and forearm mineral content in small numbers of cases [13] have shown significant increases in bone mass during such therapy.

This study provides evidence about the optimal dose of nandrolone. Clearly, when 50 mg of nandrolone is given every three weeks, the response is similar to that when it is given every 2 weeks, and the side-effects are much less.

Although the increase in bone mass in our patients may eventually be limited by an increasing absolute resorption rate (if bone mass is determined by the ratio of formation to fractional resorption [14], the increase in itself is remarkable. Most therapies for osteoporosis are expected only to limit further loss of bone, perhaps because any decrease in bone resorption they cause is followed by a decrease in bone formation [15].

Anabolic steroid therapy can only increase the bone mass if sufficient calcium is available to mineralise the new bone formed, and so in this study nandrolone was given only to patients with normal calcium absorption, or where calcium malabsorption had been corrected with calcitriol. However, anabolic steroids could possibly be beneficial even when calcium absorption is impaired, if they reduce the urine calcium, as has been reported [12].

It is interesting that the FMD rose more markedly in the patients given nandrolone alone than it did in those given combination therapy and it may be that those patients with osteoporosis and normal bone resorption have a decreased bone formation rate. This is pure speculation but it may explain their greater response to anabolic steroid therapy. It may also be relevant to this concept that adrenal androgen levels are reduced in osteoporosis [16] and perhaps nandrolone acts as a replacement for their androgen deficiency. In any case, the results reported here suggest the need for further studies of the factors governing bone formation, and ways of identifying cases in which this is grossly impaired.

References

1 Horowitz M, Need AG, Philcox JC, Nordin BEC. Effect of calcium supplementation on urinary hydroxyproline in osteoporotic postmenopausal women. Am J Clin Nutr 1984; 39: 857–859.
2 Need AG, Horowitz M, Philcox JC, Nordin BEC. 1, 25-dihydroxycalciferol and calcium therapy in osteoporosis with calcium malabsorption. Dose response relationship of calcium absorption and indices of bone turnover. Mineral Electrolyte Metab 1985; 11: 35–40.
3 Horowitz M, Need AG, Philcox JC, Nordin BEC. The effect of calcium supplements on plasma alkaline phosphatase and urinary hydroxypyrroline in postmenopausal women. Horm Metabol Res 1985; 17: 311–312.

4 Baylink DJ. Glucocorticoid-induced osteoporosis. New Engl J Med 1983; 309: 306–308.
5 Albright F, Smith PH, Richardson AM. Postmenopausal osteoporosis: its clinical features. J Am Med Assoc 1941; 116: 2465–2474.
6 Kopera H. The history of anabolic steroids and a review of clinical experience with anabolic steroids. Acta Endocrinol 1985; Suppl 271: 11–18.
7 Marshall DH, Nordin BEC. A comparison of radioactive calcium absorption tests with net calcium absorption. Clin Sci 1981; 61: 477–481.
8 Horsman A, Leach AE. The estimation of the cross-sectional area of the ulna and radius. Am J Phys Anthrop 1974; 40: 173–186.
9 Bijlsma JWJ, Duursma SA, Bosch R, Huber O. Lack of influence of the anabolic steroid nandrolondecanoate on bone metabolism. Acta Endocrinol 1982; 101: 140–143.
10 Vose GP, Keele DK, Milner AM, Rowley R, Roach TL, Sprinkle EE. Effect of sodium fluoride, inorganic phosphate and oxymetholone therapies in osteoporosis. J Gerontol 1978; 33: 204–212.
11 Chesnut CH III, Nelp WB, Baylink DJ, Denney JD. Effect of methandrostenolone on postmenopausal bone wasting as assessed by changes in total bone mineral mass. Metabolism 1977; 26: 267–277.
12 Chesnut CH III, Ivey JL, Gruber HE, Matthews M, Nelp WB, Sisom K, Baylink DJ. Stanozolol in postmenopausal osteoporosis: therapeutic efficacy and possible mechanisms of action. Metabolism 1983; 32: 571–580.
13 Dequeker J, Geusens P. Anabolic steroids and osteoporosis. Acta Endocrinol 1985; Suppl 271: 45–51.
14 Nordin BEC, Speed R, Aaron J, Crilly RG. Bone formation and resorption as determinants of trabecular bone volume in postmenopausal osteoporosis. Lancet 1981; ii: 277–279.
15 Nordin BEC, Marshall DH, Francis RM, Crilly RG. The effects of sex steroid and corticosteroid hormones on bone. J Steroid Biochem 1981; 15: 171–174.
16 Nordin BEC, Robertson AR, Seamark RF, Bridges A, Philcox JC, Need AG, Horowitz M, Morris HA, Deam S. The relation between calcium absorption, serum dehydroepiandrosterone and vertebral mineral density in postmenopausal women. J Clin Endocrinol Metab 1985; 60: 651–657.